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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
PP19768.002

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on 07/05/2007

Signature Joanne Ryan

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Application Number	Filed
10/757,708	01/14/2004

First Named Inventor: Derek O' Hagan et al.

Art Unit	Examiner
1633	Ileana Popa

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 34,297
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

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July 5, 2007
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NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 1 forms are submitted.

Reasons for requesting pre-appellate review:

Double Patenting

Various pending claims have been rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 15-19, 24-26 and 35 of O'Hagan et al. US 6,884,435 (O'Hagan).

Claim 1, the only independent claim pending, is directed to microparticles that comprise: (a) a biodegradable polymer; (b) a cationic surfactant; and (c) a first polynucleotide-containing species adsorbed on the surface of the microparticles, *wherein the adsorbed first polynucleotide-containing species constitutes at least 5 percent of the total weight of the microparticles and wherein the microparticles comprise 0.5 to 2 wt% cationic surfactant.*

The subject matter of claim1, particularly the portion italicized above, is neither taught nor suggested by the claims of O'Hagan.

The Examiner apparently recognizes this, but argues that the patent specification of O'Hagan "defines" microparticles as having a macromolecule to microparticle ratio in the range of 0.1 to 0.5% and comprising 0.5 to 1% cationic detergent surfactant, thereby meeting the italicized limitations of claim 1 above.

Appellant respectfully disagrees. Instead of defining the term "microparticles" as alleged by the Examiner, O'Hagan actually defines the term "microparticle" as being "a particle of about 100 nm to about 150 μm in diameter, more preferably about 200 nm to about 30 μm in diameter, and most preferably about 500 nm to about 10 μm in diameter." See the "Definitions" section at col. 5, lines 1-10. Nothing in O'Hagan's definition of "microparticle" pertains to the amounts of macromolecule and detergent that must be present in a particle in order for it to be termed a "microparticle," much less the amounts of *polynucleotide-containing* macromolecules and *cationic* detergent required in claim 1.

Rather than using the disclosure of O'Hagan to learn the meaning of a term in the claims, the Examiner has instead used the disclosure of O'Hagan to provide missing claim limitations (i.e., the Examiner is using O'Hagan as if it were prior art). This is impermissible in conjunction with an obviousness-type double patenting rejection. See MPEP 804.

Moreover, even assuming solely for the sake of argument that the specification were to be fully available for use in an obviousness-type double patenting rejection (and it is not), the present claims would still be patentable over O'Hagan for the reasons set forth below in conjunction with the rejection under 35 USC §102(e) based on O'Hagan.

Reconsideration and withdrawal of the outstanding nonstatutory obviousness-type double patenting rejection are requested.

Provisional Double Patenting

Various claims have been provisionally rejected under the judicially created doctrine of obviousness type double patenting as being unpatentable over certain claims of copending Application No. 11/113,861. This rejection is a *provisional* rejection. Thus, the double patenting issue has not yet matured for rational argument (i.e., the copending application has not issued as a patent and the claims may be amended/cancelled in the future). Indeed, at a future time, the provisional double patenting rejection may be the only rejection remaining in the present application, in which case the rejection will be withdrawn in accordance with the provisions of MPEP 804.

Furthermore, Serial No. 11/113,861 is a continuation of Serial No. 09/581,772, which matured as O'Hagan above. Thus the arguments set forth below in conjunction with O'Hagan can be considered for the present provisional double patenting rejection as well.

Claim rejection under 35 USC §102(e)—O'Hagan

Various claims are rejected under 35 USC §102(e) as being anticipated by O'Hagan. This rejection is traversed.

Rejections under 35 U.S.C. § 102 are proper only when the claimed subject matter is identically described in the prior art. As indicated in MPEP 2131, for a claim to be anticipated:

> ..."The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an *ipsissimis verbis* test, i.e., identity of terminology is not required. *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990)....

As noted above independent claim 1 presently requires, *inter alia*, microparticles in which an *adsorbed first polynucleotide-containing species constitutes at least 5 percent of the total weight of the microparticles*

These loadings constitute elevated loading levels relative to those previously demonstrated. By increasing polynucleotide-containing species loading levels one can, *inter alia*, reduce the amount of polymer that is administered to the a animal (for a given dose of polynucleotide-containing species). See paragraph [0006] of the present specification.

The Examiner has referred to the disclosure in Col. 13 of O'Hagan in which "macromolecules are added to the microparticles to yield microparticles with adsorbed macromolecules having a weight to weight ratio of from about 0.0001:1 to 0.25:1 macromolecules to microparticles, preferably, 0.001:1 to 0.1, more preferably 0.01 to 0.05." This passage, however, pertains generally to "macromolecules," which are defined at col. 5, lines 65 *et seq.* to refer to "without limitation, a pharmaceutical, a polynucleotide, a polypeptide, a hormone, an enzyme, a transcription or translation mediator, an intermediate in a metabolic pathway, an immunomodulator, an antigen, an adjuvant, or combinations thereof." There is no express teaching, however, that these general ranges are applicable in their entirety to each and every species embraced by the term "macromolecules,"

including polynucleotide-containing species. In fact, as seen from Example 7 of O'Hagan et al., actual loads achieved for a polynucleotide-containing species (pCMV) range from 0.84% to 2.36% for target loads of 1% to 4%.

Moreover, even assuming solely for the sake of argument that the ranges of O'Hagan are applicable in their entirety to each and every species embraced by the term "macromolecules," the ranges described are not sufficiently specific to constitute an anticipation under the statute. In this regard, the standard for anticipation is high, as noted in MPEP 2131.03:

> When the prior art discloses a range which touches *>or< overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation. In order to anticipate the claims, the claimed subject matter must be disclosed in the reference with "sufficient specificity to constitute an anticipation under the statute." What constitutes a "sufficient specificity" is fact dependent. If the claims are directed to a narrow range, >and< the reference teaches a broad range, ** depending on the other facts of the case, it may be reasonable to conclude that the narrow range is not disclosed with "sufficient specificity" to constitute an anticipation of the claims. **>See, e.g., *Atofina v. Great Lakes Chem. Corp*, 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006) wherein the court held that a reference temperature range of 100-500 degrees C did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. Further, while there was a slight overlap between the reference's preferred range (150-350 degrees C) and the claimed range, that overlap was not sufficient for anticipation. "[T]he disclosure of a range is no more a disclosure of the end points of the range than it is each of the intermediate points." *Id.* at 1000, 78 USPQ2d at 1424...

The facts of the present case are analogous to those above, if not more favorable to Applicant. As above, no specific examples falling within the claimed range are disclosed by O'Hagan. Moreover, with respect to the broad range disclosed by O'Hagan (i.e., microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.0001:1 to 0.25:1), the high "macromolecule" concentration is more than three orders of magnitude (2500 times) higher than the low macromolecule concentration (*cf.* the relatively narrow concentration ranges of claim 1 (and dependent claims 27 and 28). In this regard, please note that it was held by the Federal Circuit in *Atofina, supra*, that a much more narrow disclosure of 100-500 degrees C by a prior art reference did not describe the claimed range of 330-450 degrees C with sufficient specificity to be anticipatory. This was true even though the claimed range was *completely embraced* by the range taught in the reference. With respect to the narrow range disclosed in O'Hagan (i.e., microparticles with adsorbed macromolecules having a weight to weight ratio of from 0.01 to 0.05), there is no overlap between this range and the range of instant claim 1 (and dependent claims 27 and 28). This again is more favorable to the Applicant than *Atofina*, in which there overlap existed between the narrow range of the reference and the claimed range. Nonetheless, even this overlap was not sufficient for anticipation.

In addition to the above discussed elevated loading levels, independent claim 1 further requires, *inter alia*, microparticles that comprise *0.5 to 2 wt% cationic surfactant.* Analogous to loading of polynucleotide-containing species, there is no express teaching in O'Hagan that the broad

detergent-to-polymer ratios at col. 13 of O'Hagan are applicable in their entirety to each and every microparticle species described in the specification, including those containing cationic detergents, and even if they were, the claimed amounts of cationic detergent are not disclosed with sufficient specificity to constitute an anticipation of the claims. (See MPEP 2131.03 above and *Atofina*.) In this regard, no specific examples falling within the narrow cationic surfactant range (0.5 to 2 wt%) of claim 1 are disclosed in O'Hagan. For instance, in Example 2 of O'Hagan, 12.5 ml of a 4% PLG solution (which contains 0.5 g PLG) and a 50 ml of a 0.5% CTAB solution (which contains 0.25 g CTAB) are employed, corresponding to 50% CTAB relative to PLG. In stark contrast, in Example 1 of the present specification, 16.6 ml of a 6 % PLG solution (which contains 1 g PLG) and a solution containing 10 mg CTAB are employed, corresponding to 1% CTAB relative to PLG.

For at least these reasons, reconsideration and withdrawal of claim rejection under 35 USC §102(e) are requested.

Claim rejection under 35 USC §103(a)—Singh

Various claims are rejected under 35 USC §103(a) as being unpatentable over Singh et al., *Proc. Natl. Acad. Sci. USA*, 2000, 97:811-816 (Singh). This rejection is traversed.

As with O'Hagan, Singh doesn't teach or suggest microparticles that comprise a cationic detergent, in which an adsorbed polynucleotide-containing species constitutes at least 5 percent of the total weight of the microparticles.

For example, see Table 1 of Singh, in which loading levels of 0.92%, 0.68% and 0.62% are described. The Examiner argues that although the claimed ranges are not disclosed, it is obvious and routine in the art to vary certain parameters, including loading. As evidence of "loading optimization" in Singh, the Examiner points to Table 2 and Fig. 2. However, these data represent evidence of optimization of gene expression with respect to *dose*, rather than optimization of gene expression with respect to microparticle *loading*, which is a different concept.

Singh reports only a single procedure for forming PLG/CTAB Luc DNA microparticles (i.e., those formed by incubating 100 mg cationic microparticles in a 1 mg/ml solution of DNA--see page 812) for use therein. With only a single type of CTAB microparticle reported (i.e., those formed by the foregoing procedure), one of ordinary skill in the art would understand that in order to increase total DNA dose by a factor of 10 (see Fig. 2), the amount of the microparticle composition administered would be increased by a factor of 10, and vice versa. There is no teaching or suggestion in Singh et al. to vary the amount of DNA loading for any purpose, much less to achieve better activity as argued by the examiner.

As noted in MPEP 2144.05, a particular parameter must first be recognized as a result-effective variable before it can be argued that it is obvious to optimize the parameter, and the Examiner has presented no evidence that the claimed parameters are so recognized. For example, the

Examiner has presented no evidence (other than an unsupported allegation in the Office Action) that it is routine in the art to vary microparticle loading to achieve better activity.

Moreover, as with O'Hagan, Singh doesn't teach or suggest microparticles that comprise only 0.5 to 2 wt% cationic surfactant. For example, in forming the CTAB microparticles of Singh, 0.5 g PLG (10 ml x 5% wt/vol) is combined with 0.25 g CTAB (50 ml x 0.5% wt/vol), which corresponds to 50% CTAB relative to PLG. (*Cf.*, Example 1 of the present specification in which 16.6 ml of a 6 % PLG solution, which contains 1 g PLG, is combined with a solution containing 10 mg CTAB--corresponding to 1% CTAB relative to PLG).

Finally, as seen from Tables 3 and 4 of the present specification, microparticles with lower amounts of cationic detergent and high polynucleotide loadings like those claimed were unexpectedly found to exhibit enhanced immunogenicity, not only relative to naked DNA, but also relative to microparticles having higher amounts of cationic detergent. This is surprising, given the higher loading efficiencies observed with higher amounts of cationic detergent.

For at least the above reasons, reconsideration and withdrawal of the claim rejection under 35 USC §103(a) over Singh are requested.

Claim rejection under 35 USC §103(a)—Singh, Thalhamer, Diwan

Various claims are rejected under 35 USC §103(a) as being unpatentable over Singh and further in view of Thalhamer et al., *Endocrine Regulations*, 2001, 35:143-166 (Thalhamer) as evidenced by Diwan et al., *Journal of Controlled Release*, 2002, 85:247-262 (Diwan). This rejection is traversed.

Various deficiencies in Singh as a reference are noted above. Thalhamer and Diwan, which are cited for their teachings regarding CpG adjuvants, do not make up for those deficiencies in Singh. Therefore, claim 1 and the claims dependent upon claim 1, are patentable over these references.

Moreover, while Thalhamer and Diwan may teach CpG adjuvants, they do not teach adsorbing them to microparticles as claimed in certain claims (see, e.g., claim 8). The Examiner recognizes this, but argues that both references teach CpG in combination with DNA vaccines and that Diwan teaches that the co-delivery of CpG and antigen ***in*** *nanoparticles* is more efficient than the delivery of antigen in nanoparticles and CpG in solution. Nonetheless, it is the case that Thalhamer and Diwan do not teach or suggest the adsorption of CpG oligonucleotides to microparticles, or even nanoparticles for that matter.

For at least the above reasons, reconsideration and withdrawal of the claim rejection under 35 USC §103(a) based on Singh, Thalhamer and Diwan are requested.

Conclusion

For at least the above reasons, it is believed that the outstanding rejections to the claims are erroneous and should therefore be withdrawn.